PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 209/34, A61K 31/40
C07D 403/06, 487/10

A2

(11) International Publication Number: WO 92/07830

(43) International Publication Date: 14 May 1992 (14.05.92)

(21) International Application Number: PCT/US91/04978

(22) International Filing Date: 18 July 1991 (18.07.91)

(30) Priority data:
605,220 29 October 1990 (29.10.90) US

(60) Parent Application or Grant
(63) Related by Continuation
US 605,220 (CIP)
Filed on 29 October 1990 (29.10.90)

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

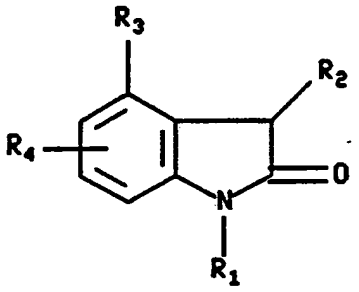
(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : NAKANISHI, Susumu [US/US]; 15 Sapia Drive, Niantic, CT 06357 (US).

(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: OXINDOLE PEPTIDE ANTAGONISTS



(I)

(57) Abstract

Oxindole peptide antagonists have formula (I), wherein R_2 is $=CH\text{-}Ar$ or spirohydantoin, and R_1, R_3 and R_4 are as defined herein. The compounds of formula (I) are of use in the treatment of small cell mammalian cancers.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU+	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE*	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

OXINDOLE PEPTIDE ANTAGONISTS

Background of the Invention

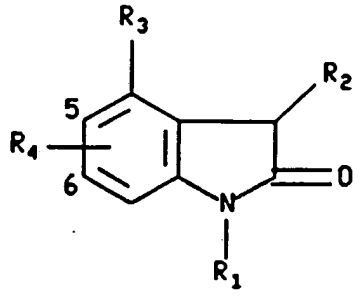
This invention relates to novel oxindole derivatives, pharmaceutical compositions containing them, and methods of administering them to a subject in need of receptor binding inhibition of gastrin releasing peptide.

Gastrin releasing peptide (GRP) is known to stimulate a wide variety of biological responses in different tissues and cell lines including mitogenesis. GRP also plays a central role in the pathophysiology of small cell lung cancer. GRP inhibitors thus have clinical utility as inhibitors of pathophysiological response to GRP in human diseases. Prior art receptor binding GRP inhibitors are peptides such as disclosed in D.C. Heimbrook et al., Peptides, Proceedings of the Eleventh American Peptide Symposium, pages 56 to 59 (1989).

The present invention provides oxindoles which are receptor binding GRP inhibitors. Oxindoles have been described in U.S. Patents 4,464,380 and 4,644,005, both of which are incorporated herein by reference, as aldose reductase inhibitors. The present oxindoles and/or their activity as receptor binding inhibition of GRP are not disclosed.

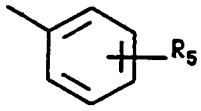
Summary of the Invention

In accordance with this invention, it has been found that certain novel oxindoles are active receptor binding inhibitors of GRP. These oxindoles have the general formula



...I

wherein R_1 is methyl, ethyl, or benzyl which is phenyl-substituted by one or two of chloro or bromo; R_2 is =CH-Ar or spirohydantoin; R_3 is C_1-C_4 alkyl, fluoro, chloro, bromo, iodo or R_4; R_4 is hydrogen, or one 5- or 6-substi- tuent as follows: $-O(CH_2)_nCONH_2$, $-O(CH_2)_nOH$, $-O(CH_2)_nCO_2H$, $-OCH_2CH(OH)CH_2OH$, or benzyloxy which is phenyl-substituted by ortho or meta carboxy, hydroxymethyl or carbamoyl; or R_4 is two substituents: one 5-substituent as defined above and 6-methyl; n is 0, 1, 2, 3 or 4; Ar is imdazolyl, thienyl, pyrrolyl, piperazinyl, naphthyl, or



wherein R_5 is one of trifluoromethyl; or two of methyl, t-butyl or hydroxy; or one of methyl with one of hydroxy; or 3,5-di(t-butyl)-4-hydroxy; with the proviso that (1) R_3 and R_4 are not both hydrogen, (2) R_1 is methyl or ethyl when R_2 is =CH-Ar, and (3) R_3 is bromo or chloro and R_1 is 3,4-dichlorobenzyl when R_2 is spirohydantoin.

Specific oxindoles of formula I are those wherein R_1 is methyl or ethyl, and those wherein R_2 is = CH-Ar in which Ar is 3,5-di(t-butyl)-4-hydroxybenzyloxy.

Other specific compounds of formula I are those wherein R_3 is methyl, those wherein R_3 is methyl and R_4 is 5-carbamoyl, 5-OCH_2CONH_2, or 5-carboxybenzyloxy, and those wherein R_3 is methyl and R_4 is 5-carbamoyl-6-methyl, 5-OCH_2CONH_2, or 5-carboxybenzyloxy-6-methyl.

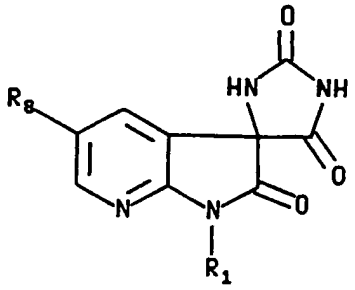
A preferred class of compounds of formula I is the class wherein R_1 is 3,4-dichlorophenyl and R_2 is spirohydantoin.

The invention is further concerned with a pharmaceutical composition having receptor binding inhibitory activity toward GRP and comprising a compound of formula I in an amount sufficient to cause receptor binding inhibition of GRP, and a pharmaceutical carrier or diluent.

The invention also resides in a method for the receptor binding inhibition of gastrin releasing peptide by adminis-

tering to a subject in need of receptor binding inhibition of gastrin releasing peptide a compound of the formula I as defined above in an amount sufficient to cause said inhibition.

The invention also resides in a method for the receptor inhibition of gastrin releasing peptide by administering to a subject in need of receptor binding inhibition of gastrin releasing peptide a compound of the formula



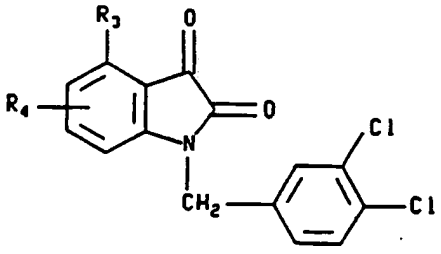
...VIII

wherein R_1 is methyl, ethyl, or benzyl which is optionally phenyl-substituted by one or two of chloro or bromo; and R_8 is bromo or chloro, in an amount sufficient to cause said inhibition.

Detailed Description of the Invention

The oxindole compounds of the invention are made by different processes depending on whether R_2 is =CH-Ar or spirohydantoin, and on whether the indole ring is 4-alkyl or 4-halo substituted.

The preparation of the oxindole compounds wherein R_2 is spirohydantoin is described in above-mentioned U.S. Patent 4,464,380. According to this method, a compound of the formula



...II

is condensed with an alkali metal cyanide such as sodium cyanide or potassium cyanide, to form the corresponding spirohydantoin oxindole wherein R_3 is chloro or bromo, and R_4 is as defined in connection with formula I. This condensation is generally carried out in the presence of a reaction-inert polar organic solvent in which both the reactants and the reagents are miscible. Preferred polar organic solvents include cyclic ethers such as dioxane and tetrahydrofuran, lower alkylene glycols such as ethylene glycol and trimethylene glycol, water-miscible lower alkanols such as methanol, ethanol and isopropanol, and N,N-di(C_1-C_4 lower alkyl)C_1-C_4 lower alkanoamides such as N,N-dimethylacetamide and N,N-dimethylacetamide. The reaction is generally conducted at a temperature of from about 50 to about 150C for a period of time of about two hours to four days. Although the amount of reactant and reagents used may vary, it is preferable to use a slight molar excess of the alkali metal cyanide reagent with respect to the carbonyl ring starting material of formula II to obtain maximum yield.

The compounds of formula I wherein R_2 is =CHAr may be prepared as depicted in Reaction Scheme I. R_1, R_3, R_4 and Ar in formulae III and IV of the Scheme are as defined above in connection with formula I.

The reaction of the oxindoles of formula III with the aldehydes of formula IV is generally conducted in a reaction-inert solvent. Suitable solvents include aromatic amines such as pyrrolidone or pyridine, aliphatic amines such as tetrahydrofuran, and alcohols such as methanol, ethanol, propanol and t-butanol. In a preferred method, the reaction solvent is methanol and pyrrolidine. The reaction is in general conducted at temperatures of from about -10C to about 80C. A preferred reaction temperature is room temperature.

The oxindole of formula III is advantageously first dissolved in a reaction-inert polar solvent such as a C_1-C_6

lower alkanol, e.g. methanol, before being combined with the aldehyde of formula IV.

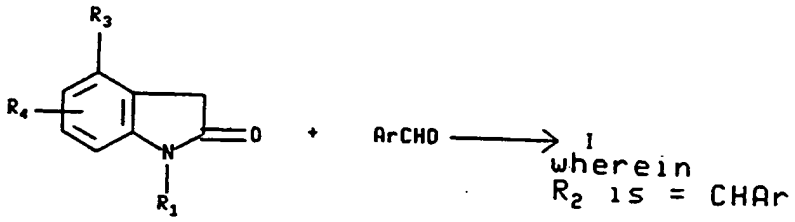
The reaction of compounds III with compounds IV is conducted in the presence of a base. Suitable bases are alkali metal hydroxides such as sodium hydroxide, and organic bases such as pyrrolidine and pyridine. A preferred base is pyrrolidine.

Alternatively, the compounds of formula I wherein R_2 is =CHAr may be prepared as depicted in Scheme II. R_1, R_3 and Ar in the formulae IV, V and VI of the Scheme are as defined above with reference to compounds of formula I. R_5 in formula VII is $(CH_2)_nCONH_2$, $(CH_2)_nOH$, $(CH_2)_nCO_2H$, $CH_2CH(OH)CH_2OH$, or benzyl substituted by ortho or meta carboxy, hydroxymethyl or carbamoyl. X in formula VII is halide such as chloride.

The reaction of the N-R_1-hydroxy-indoles of the formula V with the aldehyde of formula IV proceeds as described above with reference to Reaction Scheme I.

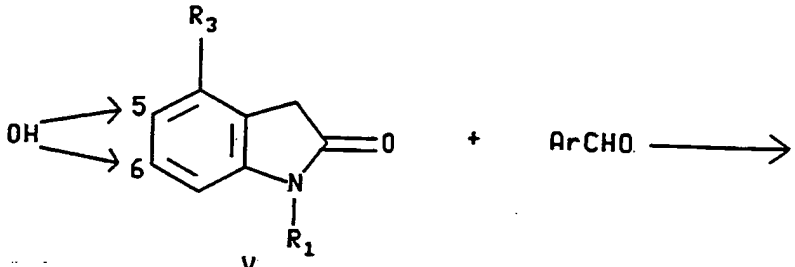
The reaction of compounds VI with compounds VII proceeds in the presence of a catalyst. Suitable catalysts are lithium bis(trimethylsilyl)amide, lithium bis(dimethylphenylsilyl)amide, lithium t-butyl(tri(C_1-C_6)alkylsilyl)-amide and lithium hexamethyldisilylamide. A preferred catalyst is lithium bis(trimethylsilyl)amide. The reaction temperature ranges in general from about -78C to about 10C. A preferred reaction temperature range is from about -40 to -30C. The reaction generally proceeds in the presence of a reaction-inert solvent. Suitable solvents are dimethylformamide, dimethylacetamide, tetrahydrofuran-ethyleneglycoldimethyl ether. The preferred solvents are dimethylformamide and dimethylacetamide.

Reaction Scheme I

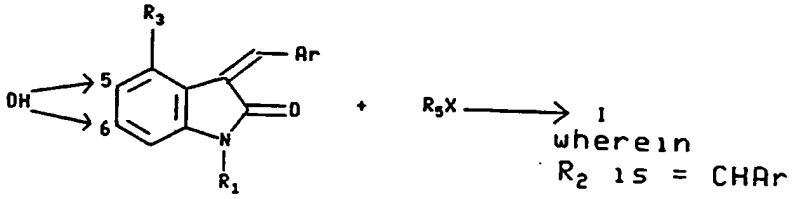


III IV

Reaction Scheme II



V IV



VI VII

The starting material of formula V may be prepared by known methods. For instance, N-methyl-N-chloroacetyl-p-anisidine may be reacted with aluminum trichloride to form N-methyl-5-hydroxyoxindole.

The starting material of formula III may be prepared from the hydroxyindoles of formula V by reaction with compounds of formula VII as described above for the reaction of formula VI in Reaction Scheme II.

The compounds of formula VIII may be prepared as disclosed in U.S. Patent 4,464,380.

The novel compounds of formula I and the compounds of formula VIII are useful in the treatment of human diseases

resulting from pathophysiological responses to GRP, e.g. the treatment of small cell lung cancer, the treatment of central nervous system disorders such as psychosis, panic disorders and mania, the treatment of gastrointestinal diseases such as gastric ulcers, and the treatment of eating disorders such as anorexia and bulimia.

The compounds of the invention may be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally or in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They can be injected parenterally, for example, intramuscularly, intravenously or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which can contain other solutes, for example, enough salt or glucose to make the solution isotonic.

The invention also provides pharmaceutical compositions comprising an effective amount of a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier.

The compounds of the invention can be administered to humans for the treatment of diseases by either the oral or parenteral routes, and may be administered orally at dosage levels of about 0.1 to 500 mg/kg/day, advantageously 0.5-50 mg/kg/day given in a single dose or up to 3 divided doses. For intramuscular or intravenous administration, dosage levels are about 0.1-200 mg/kg/day, advantageously 0.5-50 mg/kg/day. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. Variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of

administration chosen as will be known to those skilled in the art.

The activity of the present compounds in the receptor binding inhibition of GRP may be demonstrated by the following in vivo test. Small cell lung carcinoma derived cells are implanted subcutaneously into athymic mice. These animals receive a test compound at specified time intervals to inhibit tumor growth. Non-treated mice succumb to the invading cells. In vitro activity of a test compound may be determined in an in vitro receptor binding assay using membranes of cells derived from small lung cell carcinoma.

The following examples illustrate the invention.

Example 1

A. N-chloroacetyl-N-methylanisidine

To a solution of 5.98 ml of chloroacetylchloride in 68 ml of methylene dichloride under nitrogen at -10C was dropwise added a mixture of N-methyl-anisidine (9.3 g) and diisoproylethylamine (14.2 ml) in 20 ml of methylenedichloride. The resulting mixture was allowed to warm up to room temperature and stirred at room temperature for 7 hours. Water (30 ml) was added and the organic layer was separated. Water (30 ml) was added again, and the mixture was acidified to pH 2 with hydrochloric acid, stirred for 15 minutes and extracted with methylene dichloride. The organic layer was separated, washed, dried and evaporated to give the title compound, 11.5 g(79%), m/e 213 (mass spec).

B. N-methyl-5-hydroxyindole

To a 500 ml three neck flask containing 11.49 g of N-chloroacetyl-N-methyl-anisidine was added 15.78 g (0.118 mol, 2.2 mol equivalent) of $AlCl_3$ at room temperature under nitrogen. The mixture was stirred with a mechanical stirrer and gradually heated to 220C. At 47C a strong gas stream appeared. Fifteen minutes later, the mixture equilibrated at 221C and the stirring was continued at that temperature for two hours. After cooling to room temperature, ice water (200 ml) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was

filtered and the cake washed with water. The wet cake was recrystallized from ethylacetate and dried to provide 590 mg of title product, m.p. 198-199C(dec.). Mass spectrum m/e 163.

C. 1-Methyl-3-methylene-[3', 4'-di-tertiary-butyl-4'-hydroxy]-5-hydroxy oxindole

To a solution of 1-methyl-5-hydroxy oxindole (2 g, 12 mmole) in 60 ml of methanol was added 1.02 ml (12 mmoles) of pyrrolidine followed by 2.86 g (12 mmoles) of 3,5-di-tert-butyl-4-hydroxy-benzaldehyde, and the resulting mixture was stirred at room temperature overnight. Then the reaction mixture was poured into a mixture of 100 ml of ice-water and 200 ml of 1N HCl. The solid formed was collected by filtration and dried to give the title compound of 3.5 g (78%), m.p. 136-140C(dec.). Mass spec. m/e 379, NMR (DMSO) 8.5 and 9 ppm (2H of OH), 6.7 7.2 ppm (aromatic 5H), 3.4 ppm (3H of CH_3 and 1.5 ppm (18H of tert-butyl).

D. 1-Methyl-[3-methylene-(3',5'-tert-butyl-4'-hydroxy-phenyl)-5-(2'-carbomethoxybenzyloxy)indole.

The title compound of step C (1.2 g, 3.16 mmoles), was dissolved in 12.4 ml of dimethyl formamide and cooled to -40C under nitrogen. Then lithium bis(trimethylsilyl) amide, (6.95 ml, 6.95 mmoles) was added and the mixture stirred at -40C for five minutes. To the resulting mixture was dropwise added 1.08 g (3.79 mmoles) of 2-bromoethyl benzoic acid methyl ester. The cooling bath was then removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of 100 ml of water and 200 ml of 1N HCl, then extracted into ethyl acetate. The organic layer was separated, washed with water and saturated NaCl aqueous solution, dried over anhydrous magnesium sulfate, filtered and evaporated to give the crude product, 1.6 g. Purification via silica gel column chromatography gave the fractions eluted with chloroform 820 mg (49%), m.p. 159-162C(dec.). Mass spec. m/e 527, NMR($CDCl_3$) 6.8-8.2

ppm(aromatic 9H), 4.9 and 5.2 ppm(3H, OH and CH_2), 3.9 ppm(3H of $OCOCH_3$), 3.3 ppm(3H of N-CH_3) and 1.4 ppm(9H of tert-butyl).

E. 1-Methyl-3-methylene[3',4'-di-tert-butyl-4'--hydroxy-phenyl]-5-(2'-carboxybenzyloxy)-indole.

The title compound of step D (400 mg, 0.76 mmole) was hydrolyzed by dissolving in 3.8 ml of tetrahydrofuran, adding 3.8 ml of methanol and then introducing 3.8 ml of 6N NaOH. The resulting mixture was stirred at room temperature overnight, and then poured into a mixture of 100 ml of water and 100 ml of 1N HCl. The precipitates formed were collected by filtration, washed with water, and dried to give the desired compound, 350 mg (90%), m.p. 124-125C. Mass spec. m/e 513. Analysis, calcd. for $C_{32}H_{35}NO_5$; C=74.81, H=6.87, N=2.73; found C=74.68, H=6.28, N=2.53.

Example 2

A. 1-Methyl-3-methylene-[3',4'-di-tert-butyl-4'-hydroxy]-5-hydroxy oxindole

To a solution of 1-methyl-5-hydroxy oxindole (2 g, 12 mmole) in 60 ml of methanol was added 1.02 ml (12 mmoles) of pyrrolidine, followed by 2.86 g (12 mmoles) of 3,5-di-tert-butyl-4-hydroxy-benzaldehyde. The resulting mixture was stirred at room temperature overnight. Then the reaction mixture was poured into a mixture of 100 ml of ice-water and 200 ml of 1N HCl. The solid formed was collected by filtration and dried to give the title compound: 3.5 g (78%), m.p. 136-140C (dec.). Mass spec. m/e 379. NMR (DMSO):8.5 and 9 ppm (2H of OH), 6.7 7.2 ppm (aromatic 5H), 3.4 ppm(3H of CH_3) and 1.5 ppm(18H of tert-butyl).

B. 1-Methyl-[3-methylene-(3',5'-tert-butyl-4'-hydroxy-phenyl)-5-(2'carbomethoxybenxyloxy)indole.

The compound of step A (1.2 g, 3.16 mmoles) was dissolved in 12.4 ml of dimethyl formamide and cooled to -40C under nitrogen. Then lithium bis(trimethylsilyl) amide (6.95 ml, 6.95 mmoles) was added and the mixture was stirred at -40C for five minutes. To the resulting mixture was

added dropwise 1.08 g (3.79 mmoles) of 2-bromoethyl benxoic acid methyl ester. After the addition, the cooling bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of 100 ml of water and 200 ml of 1N HCl and extracted into ethyl acetate. The organic layer was separated, washed with water and saturated NaCl aqueous solution, and dried over anhydrous magnesium sulfate, filtered and evaporated to give the crude product, 1.6 g. Purification via silica gel column chromatography gave the fractions eluted with chloroform, 820 mg (49%), m.p. 159-162C (dec.). Mass spec. m/e 527. NMR ($CDCl_3$): 6.8-8.2 ppm (aromatic 9H), 4.9 and 5.2 ppm(3H, OH and CH_2), 3.9 ppm(3H of $OCOCH_3$), 3.3 ppm (3H of $N-CH_3$) and 1.4 ppm(9H of tert-butyl).

C. 1-Methyl-3-methylene[3',4'-di-tert-butyl-4'hydroxy-phenyl]-5-(2'carboxybenzyloxy)-indole.

The benxoyloxy ester of step B (400 mg, 0.76 mmole) was hydrolyzed by dissolution in 3.8 ml of tetrahydrofuran and addition of 3.8 ml of methanol. Then, 3.8 ml of 6N NaOH was introduced. The resulting mixture was stirred at room temperature overnight and then poured into a mixture of 100 ml of water and 100 ml of 1N HCl. Precipitate formed was collected by filtration, washed with water and dried to give the desired compound, 350 mg (90%), m.p. 124-125C. Mass spec. m/e 513. Analysis, calcd. for $C_{32}H_{35}NO_5$: C=74.81, H=6.87, N=2.73; found C=74.68, H=6.28, N=2.53.

Example 3

According to the process of Example 2, the following compounds of formula I are prepared.

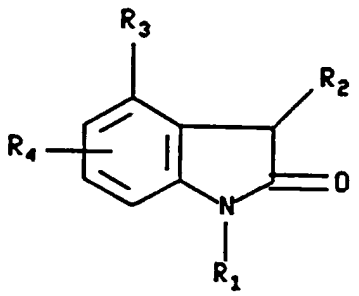
Table

R_1	R_2	R_3	R_4	m.p.	Calcd.		Found
C_2H_5	methylene-(3,5-di-tbutyl-4-hydroxyphenyl)	2-carboxy-benzyloxy	H	173-174°C	$C_{33}H_{37}O_5N$ MW 527.63	C=75.12 H= 7.97 N= 2.65	75.03 7.09 2.49
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(2-carboxy-benzyloxy)	163-164°	$C_{31}H_{33}NO_5$ MW 499.58	C=74.52 H= 6.66 N= 2.80	74.55 6.53 2.62
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	6-(2-carboxy-benzyloxy)	110-111°C	$C_{33}H_{37}O_5N$ MW 527.63	C=75.12 H= 7.07 N= 2.65	75.68 7.05 2.27
CH_3	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(2-carboxy-benzyloxy)	124-125°C	$C_{32}H_{35}NO_5$ MW 513.61	C=74.81 H= 6.87 N= 2.73	74.68 6.28 2.53
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(CH_2OH-O-)	230-231°C(dec)	$C_{26}H_{33}O_4N$ MW 423.53	C=73.73 H= 7.85 N= 3.31	73.96 7.30 3.15
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(CO_2H-C_3H_6-O-)	133-135°C(dec)	$C_{29}H_{37}O_5N$ MW 479.59	C=72.62 H= 7.78 N=2.92	72.89 7.48 2.87
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(CH_2OH-CH_2-O-)	113-114°C	$C_{27}H_{35}O_4N$ MW 437.56	C=74.11 H= 8.06 N= 3.20	74.38 7.83 3.00
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(2-$NH_2C(O)$ CH_2-O-benzyl-oxy)	129-130°C(dec)	$C_{28}H_{36}N_2O_4$ MW 464.59	C=72.38 H= 7.81 N= 6.03	72.88 7.84 6.37

R_1	R_2	R_3	R_4	m.p.	Calcd.		Found
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(2-carboxy-benzyloxy)	123-124°C	$C_{34}H_{39}NO_5$	C=72.96	73.76
						H= 7.38	7.46
					MW 541.66	N= 2.50	2.41
C_2H_5	methylene-(3,5-di-methyl-4-hydroxyphenyl)	H	5-(2-hydroxy-methylbenzyloxy)	129-130°C	$C_{27}H_{25}O_5N$	C=73.12	73.30
						H= 5.68	5.63
					MW 443.48	N= 3.16	3.04
C_2H_5	methylene-(3,5-di-t-butyl-phenyl)	2-carboxy-benzyloxy	H	oil	$C_{33}H_{37}NO_4$	C=77.46	77.11
						H= 7.29	8.53
					MW 511.63	N= 2.74	2.12
CH_3	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	-O-CH_2OH	230-231°(dec)	$C_{25}H_{31}O_4N$	C=73.32	73.35
						H= 7.63	7.62
					MW 409.51	N= 3.42	3.48
C_2H_5	methylene-(4,5-dichloro-phenyl)	H	5-(2-carboxyl-benzyloxy)	244-245°C	$C_{25}H_{19}O_4NCl_2$	C=64.11	63.82
						H= 4.09	3.90
					MW 468.31	N= 2.99	2.89
C_2H_5	methylene-(2-pyrrolyl)	H	5-(2-carb-oxylbenzyloxy)	210-211°C	$C_{23}H_{20}N_2O_4$	C=71.12	71.09
						H= 5.19	5.10
					MW 388.41	N= 7.21	7.05
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl) (intermediate)	CH_3	OH	218-219°C	$C_{26}H_{33}NO_3$	C=76.62	75.60
						H= 8.16	7.89
					MW 407.53	N= 7.89	3.34
C_2H_5	methylene-(3,5-di-t-butyl-4-hydroxyphenyl)	H	5-(2-carb-oxylbenzyloxy)	180-181°C	$C_{33}H_{37}NO_5$	C=75.12	75.10
						H= 7.07	7.06
					MW 527.63	N= 2.65	2.63

CLAIMS

1. A compound of the formula



...I

wherein

R_1 is methyl, ethyl, or benzyl which is phenyl-substituted by one or two of chloro or bromo;

R_2 is =CH-Ar or spirohydantoin;

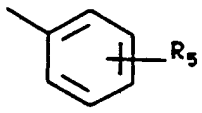
R_3 is C_1-C_4 alkyl, fluoro, chloro, bromo, iodo or R_4;

R_4 is hydrogen, or one 5- or 6-substituent as follows $-O(CH_2)_nCONH_2$, $-O(CH_2)_nOH$, $-O(CH_2)_nCO_2H$, $-OCH_2CH(OH)CH_2OH$, or benzyloxy which is phenyl-substituted by ortho or meta carboxy, hydroxymethyl or carbamoyl; or

R_4 is two substituents: one 5-substituent as defined above and 6-methyl;

n is 0, 1, 2, 3 or 4;

Ar is imidazolyl, thienyl, pyrrolyl, piperazinyl, naphthyl, or



wherein

R_5 is one of trifluoromethyl; or two of methyl, t-butyl or hydroxy; or one of methyl with one of hydroxy; or 3,5-di(t-butyl)-4-hydroxy; with the proviso that (1) R_3 and R_4 are not both hydrogen, (2) R_1 is methyl or ethyl when R_2 is =CH-Ar, and (3) R_3 is bromo or chloro and R_1 is 3,4-dichlorobenzyl when R_2 is spirohydantoin.

2. A compound according to claim 1 wherein R_1 is methyl or ethyl.

3. A compound according to claim 2 wherein R_2 is =CH-Ar in which Ar is 3,5-di(t-butyl)-4-hydroxybenzyloxy.

4. A compound according to claim 3 wherein R_3 is methyl.

5. A compound according to claim 4 wherein R_4 is 5-carbamoyl, 5-OCH_2CONH_2, or 5-carboxybenzyloxy.

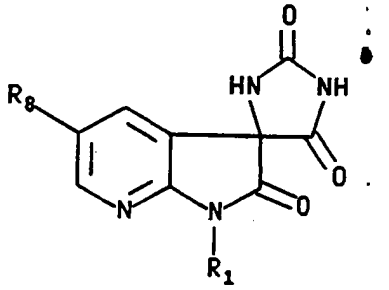
6. A compound according to claim 5 wherein R_4 is 5-carbamoyl-6-methyl, 5-OCH_2CONH_2-6-methyl, or 5-carboxybenzyloxy-6-methyl.

7. A compound according to claim 1 wherein R_1 is 3,4-dichlorophenyl, and R_2 is spirohydantoin.

8. A pharmaceutical composition comprising a compound of the formula I as defined in claim 1 in a pharmaceutically sufficient amount, and a pharmaceutical carrier or diluent.

9. A method for the receptor binding inhibition of gastrin releasing peptide which comprises administering to a subject in need of receptor binding inhibition of gastrin releasing peptide a compound of the formula I as defined in claim 1 in an amount sufficient to cause said inhibition.

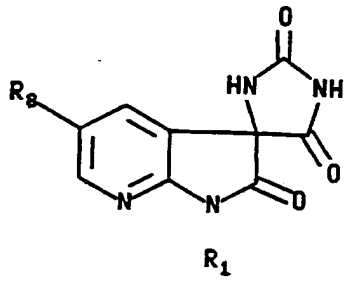
10. A method for the receptor binding inhibition of gastrin releasing peptide which comprises administering to a subject in need of receptor binding inhibition of gastrin releasing peptide a compound of the formula



...VIII

wherein R_1 is methyl, ethyl, or benzyl which is optionally phenyl-substituted by one or two of chloro or bromo; and R_8 is bromo or chloro, in an amount sufficient to cause said inhibition.

11. A method for the treatment of small lung cancer, central nervous system disorders, gastrointestinal diseases or eating disorders which comprises administering to a subject in need of such treatment an amount, effective in such treatment, of a compound of the formula I as defined in claim 1 or a compound of the formula

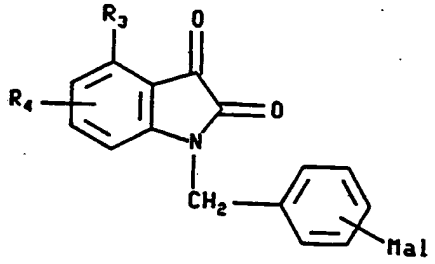


...VIII

wherein R_1 is methyl, ethyl, or benzyl which is optionally phenyl-substituted by one or two of chloro or bromo; and R_8 is bromo or chloro.

12. A process for preparing a compound of the formula I as defined in claim 1 which comprises

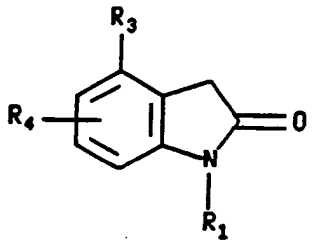
reacting a compound of the formula



...II

wherein R_3 and R_4 are as defined in claim 1 and Hal is one or two of chloro or bromo, with an alkali metal cyanide to obtain compounds of formula I wherein R_2 is spirohydantoin and R_1 is benzyl which is phenyl-substituted by one or two of chloro or bromo; or

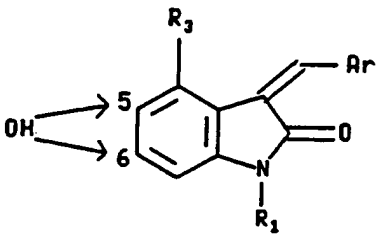
reacting a compound of the formula



III

with an aldehyde of the formula ArCHO wherein Ar is as defined in claim 1 to obtain compounds of formula I wherein R_2 is =CH-Ar and R_1, R_3 and R_4 are as defined in claim 1; or

reacting a compound of the formula



VI

wherein R_1, R_3 and Ar are as defined in claim 1 with a halide of the formula R_5X wherein R_5 is $(CH_2)_nCONH_2$, $(CH_2)_nOH$, $(CH_2)_nCO_2H$, $CH_2CH(OH)CH_2OH$, or benzyl substituted by ortho or meta carboxy, hydroxymethyl or carbamoyl and X is halo.